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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/328,975	06/09/1999	JOHN A. WOLFF	MIRUS009	7574

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EXAMINER

SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/328,975	Applicant(s) WOLFF ET AL.	
	Examiner Richard Schnizer, Ph. D	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 December 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-8,10,12-14 and 19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-5,7,8,10,12-14 and 19 is/are rejected.
- 7) ☒ Claim(s) 6 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 June 1999 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

An amendment was received and entered on 12/11/03.

Claims 15-18 were canceled as requested.

Claims 1, 3-8, 10, 12-14, and 19 remain pending and are under consideration in this Office action.

Compliance with 37 CFR 1.121

Applicant is reminded that 37 CFR 1.121 requires that all matter added to claims must be indicated by underlining. In the response filed 12/11/03 step b) of claim 1 was amended by addition of the words "ionically", "step a)", and "form a new complex having a net charge more negative than the complex in step a)", but these additions were not underlined. In addition claim 5 while indicated as "previously amended", contained the underlined phrase "succinylated PLL". This term was already present in claim 5 and was not added matter. Applicant is reminded that failure to comply with 37 CFR 1.121 may result in issuance of a notice of noncompliant amendment.

Rejections Withdrawn

The rejections under 35 USC 102 of claims 8, 10, 12, 14-16, and 18 as being anticipated by Erbacher et al (Drug Deliv. 4:173-179, 1997), claims 8, 10, 12, 14 and 19 as being anticipated by Gao et al (HUMAN GENE THERAPY, (1993 Feb) 4 (1) 17-24) or Kupfer et al (HUMAN GENE THERAPY, (1994 Dec) 5 (12) 1437-43), claims 8, 10, 12, 14 and 19 as being anticipated by Boussiff et al (Proc. Nat. Acad. Sci. 92:7997-

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7301, 8/1995), claims 8, 10, 12 and 14 as being anticipated by Kabanov et al (US Patent 5,656,611, issued 8/12/97), and claims 8, 10, 12, and 14 as being anticipated by Baker et al (Nucl. Acids Res. 25(10): 1950-1956, 5/1997) are withdrawn in view of Applicant's amendments.

After further consideration, the rejection of claims 8, 10, 12, and 14 as being anticipated by Katayose et al (Bioconj. Chem. 8:702-707, 1997) is withdrawn because the anticipatory structure in Katayose was a transient intermediate complex disclosed only in a schematic diagram and formed during a cooperative transition between two different complexes. Figures 6 and 7 of Katayose, electrophoretic gels of compositions resulting from addition of a polyanionic polymer to a polycation/nucleic acid complex, provide no evidence for any stable intermediate complex comprising three polymeric species.

Claim Objections

Claim 1 is objected to because it requires "associating a charged polymer to the complex of step (a)". Substitution of the word "with" for the word "to" is suggested.

Claim 3 is objected to because it contains the acronyms PLL and PEI. Applicant should amend the first claim containing a given acronym to contain the full name of what is implied by the acronym, followed parenthetically by the acronym.

Claim Rejections - 35 USC § 112

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 8, 10, and 12-14 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 8, 10, and 12-14 require a polyanionic polymer having a molecular weight of "at least 30 kDa". The specification contains no written support for this amendment, so it constitutes new matter. At the time of the amendment (filed 2/14/03), Applicant pointed for support to Example 1, beginning on page 22, line 25. This example discloses a the polyanionic polymers polyglutamic acid (49 kDa), polyaspartic acid (36 kDa), succinylated PLL (no molecular weight given), and pCILuc (no molecular weight given). Nowhere in this section is there any support for the genus of all polyanionic polymers having a molecular weight of at least 30 kDa. Thus the amendment constitutes new matter.

Response to Arguments

Applicant's arguments filed 12/11/03 have been fully considered but they are not persuasive. Applicant argues essentially that disclosure of the polyanionic polymers polyglutamic acid (49 kDa), polyaspartic acid (36 kDa), succinylated PLL (made from 34

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kDa PLL, greater than no molecular weight given), and pCILuc (which Applicant asserts is 975 kDa), heparin, dextran sulfate, and PEGylated-SPLL provides adequate written description of the genus of all polyanionic polymers having a molecular weight of at least 30 kDa.

This is unpersuasive because the specification as filed does not support the notion that Applicant contemplated excluding from the claimed invention the subgenus of polyanionic polymers with a molecular weight lower than 30 kDa. The specification provides no guidance as to any preferred molecular weight range of the subgenus of polyanionic polymers, instead defining only what is meant by the generic term "polymer". See page 7, lines 11-16 which states that a polymer is:

"a molecule built up by repetitive bonding together of smaller units called monomers. In this application the term polymer includes both oligomers which have two to about 80 monomers and polymers having more than 80 monomers."

Because the specification provides no support for any preferred range of molecular weights for the specific subgenus of polyanionic polymers, the definition of "polymers" cited above can be applied to the subgenus of polyanionic polymers. As such, this passage supports a range of polyanionic polymers from 2 units to greater than 80 units. This shows that Applicant contemplated polymers of less than 30 kDa, because the specification discloses no monomer that would provide a 30 kDa polymer that comprises only 2-80 monomers. Further, the specification as filed provides no literal support for the arbitrary lower range limit of 30 kDa. With regard to numerical range limitations MPEP 2163.05 teaches that the new matter analysis "must take into account which ranges one skilled in the art would consider inherently supported by the

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discussion in the original disclosure. In the decision in *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25%- 60%" and specific examples of "36%" and "50%." A corresponding new claim limitation to "at least 35%" did not meet the description requirement because the phrase "at least" had no upper limit and caused the claim to read literally on embodiments outside the "25% to 60%" range, however a limitation to "between 35% and 60%" did meet the description requirement." In light of this finding, explicit disclosure of polymers of 36 and 39 kDa, inherent disclosure of 975 kDa 49, and vague disclosure a polyanionic that was 34 kDa before the addition of an unknown amount of conjugate, do not provide support for the subgenus of polyanionic polymer with a molecular weight of "at least 30 kDa", and the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 4, 5, 7, and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee et al (US Patent 5,907,777).

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Lee teaches methods for delivering a nucleic acid complex to cells, in which complexes are formed between polycations and nucleic acids. The charge of these complexes may be readjusted by addition of polyanionic polymers such as polyglutamic acid or polymethacrylic acid. See paragraphs 12 (in part) and 13, reproduced below:

12 **It also is possible, pursuant to the present invention, to affect the charge balance of a complex via other "helper" molecules, i.e., molecules that contribute a charged species or that sequester a charged species in the reaction mixture. Examples of suitable anionic helper molecules include (1) non-monovalent anions such as PO.sub.4.sup.3-, HPO.sub.4.sup.2-, EDTA, DTPA, and deferoxamine, (2) anionic polymers such as polymethacrylic acid and poly glutamic acid, and (3) anionic detergents such as cholesteryl hemisuccinate (CHEMS), cholate, fatty acids and deoxycholate**

13 **After the nucleic acid/polycation complex is formed, it often is useful to bring the complex back to near charge neutrality. This can be achieved, as described above, by addition of an acid or base and by removal or neutralization of a helper molecule.**

The resulting ternary complexes are then associated with anionic lipids for delivery in vivo. Note that this step is not excluded by the instantly rejected claims. Thus Lee anticipates the claims

Claims 1, 3, 4, 5, 7, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al (WO 97/00965, published 1/9/97).

Lee teaches methods for delivering a nucleic acid complex to cells, in which complexes are formed between polycations and nucleic acids. The charge of these complexes may be readjusted by addition of polyanionic polymers such as polyglutamic acid or polymethacrylic acid. See page 11, lines 1-11 and 28-32 which provide the same disclosure of US Patent 5,907,777, above.

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Claims 8, 10, 12, and 14, and stand rejected under 35 U.S.C. 102(e) as being anticipated by Wolff et al (US Patent 6,339,067, filed 12/30/97).

Wolff teaches complexes comprising plasmid DNA and polycations. The complexes may also comprise a second polyanionic. See e.g. column 21, lines 48-56, and column 28, lines 1-61. Disclosed polycations include histones, protamines, polylysine, polyarginine, polyornithine, DEAE dextran, polybrene, and polyethylenimine. See e.g. column 1, lines 21-26. Disclosed polyanions include dextran sulfate (molecular weight = 500 kDa), and the specification teaches that other polyanions could be used. See column 28, lines 37-40, and column 29, lines 1-3.

Thus Wolff anticipates the claims.

Response to Arguments

Applicant's arguments filed 12/11/03 have been fully considered but they are unpersuasive.

Applicant argues that "Wolf et al. in column 21 does not teach a second polyanion. Instead, Wolff et al. teaches the formation of a DNA/polycation complex in HEPES buffer containing the chelating agent EDTA and then crosslinking the polycation with the bifunctional crosslinking reagent DTBP. No mention is made of a second polyanion in this section. Applicants believe that the amended claims are not anticipated by binary complexes."

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Applicant's attention is directed to the rejection of record mailed 6/17/03, essentially reproduced above, which clearly refers to column 28, lines 1-61 of the Wolff patent. This passage teaches in part that

"After the obtaining soluble particles of positively-charged caged DNA/PLL complexes their surface was rendered negatively charged by complexing it with the excess of polyanion. It was found that upon addition of polyanion solution to soluble DNA/PLL complex the net charge of the triple complex can be changed to the opposite at the certain concentration of the polyanion"

Applicant has failed to consider this portion of the rejection, which clearly shows that Wolff teaches a second polyanion and meets the limitations of the claims. For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3-5, and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al (US Patent 6,339,067, filed 12/30/97).

Wolff teaches methods of recharging cationic nucleic acid delivery compositions. DNA polycation complexes were prepared, and then polyanions were added to the complexes in order to form a new complex with a less positive net charge. See e.g. column 21, lines 48-56, and column 28, lines 1-61. Disclosed polycations include histones, protamines, polylysine, polyarginine, polyornithine, DEAE dextran, polybrene,

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and polyethylenimine. See e.g. column 1, lines 21-26. Disclosed polyanions include dextran sulfate (molecular weight = 500 kDa), and the specification teaches that other polyanions could be used. See column 28, lines 37-40, and column 29, lines 1-3.

Wolff does not exemplify delivery of the complexes to cells in vitro or in vivo. It would have been obvious to one of skill in the art to deliver the complexes of Wolff to cells in vivo. One would have been motivated to do so because Wolff teaches that the complexes are intended to be used to transfer nucleic acids to cells in vivo. See column 4, lines 66 and 67, and column 11, lines 15-19.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 2/19/03 have been fully considered but they are unpersuasive.

Applicant addresses this rejection at page 8 of the response. Applicant asserts the opinion that "that the teaching of Wolff et al., at column 28, is that caged DNA/polycation complexes are more stable than uncaged DNA polycation complexes." Applicant goes on to note that " appears to argue that "[p]olyanions are utilized by Wolff et al. to compete with DNA interaction with polycations. This competition provided a means to measure stability of caged vs. uncaged DNA/polycation complexes."

Inasmuch as this might amount to an argument against the rejection, it is unpersuasive because Applicant has not addressed the issue of whether or not Wolff

teaches that the complexes are intended to be used to transfer nucleic acids to cells in vivo. In light of column 11, lines 15-19 of Wolff which state:

In a preferred embodiment, stable caged polyion particles still bear a net positive charge. However, it is desirable to recharge it so it would interact less with negatively-charged polymers and particles in vivo. Recharging is switching the net polyion particle charge to an opposite charge.

In light of this passage it is clear that recharged caged polyion particles are specifically intended for use in vivo, and the rejection is maintained.

Conclusion

No claim is allowed. Claim 6 is objected as depending from a rejected claim, but would be allowable if rewritten as an independent claim incorporating all of the limitations of the claim from which it depends. Claim 13 is free of the prior art of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.



DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.